Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Nevirapine and Hepatic/Rash Toxicity (Updated September 14, 2011)

Panel's Recommendations
• Nevirapine-based regimens should be initiated in women with CD4 counts >250 cells/mm^3 only if the benefits clearly outweigh the risks because of the drug's potential for causing hepatic toxicity/hypersensitivity reaction **(AII)**.
• Women who become pregnant while receiving nevirapine-containing regimens and who are tolerating the regimen well can continue on the therapy regardless of CD4 count **(AII)**.

Increases in hepatic transaminase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) associated with rash or systemic symptoms may be observed during the first 18 weeks of treatment with nevirapine. Signs and symptoms of systemic toxicity may be nonspecific and can include fatigue, malaise, anorexia, nausea, jaundice, liver tenderness, or hepatomegaly, with or without initially abnormal hepatic transaminases[1]. The development of severe nevirapine-associated skin rash has been reported to be 5.5–7.3 times more common in women than men and has been reported in pregnant women[2-3]. Other studies have found that hepatic adverse events with systemic symptoms (predominantly rash) were 3.2-fold more common in women than in men[4-5]. The degree of risk of rash and hepatic toxicity also appears to vary with CD4 cell count. In a summary analysis of data from 17 clinical trials of nevirapine therapy, women with CD4 cell counts >250 cells/mm^3 were 9.8 times more likely than women with lower CD4 cell counts to experience symptomatic, rash-associated, nevirapine-related hepatotoxicity[4]; a single-center study also found higher CD4 cell counts to be associated with increased risk of severe nevirapine-associated skin rash[2]. CD4 cell counts >250 cells/mm^3 predicted rash illness, but not liver enzyme elevation, among pregnant and nonpregnant women initiating nevirapine-based combination antiretroviral (ARV) regimens in three U.S. university clinics[6]. Other international cohorts of nonpregnant women have experienced hepatotoxicity and rash at similar rates as in U.S. studies, but not in association with CD4 cell counts >250 cells/mm^3 [7]. In general, in controlled clinical trials, hepatic events, regardless of severity, have occurred in 4.0% (range 0%–11.0%) of patients who received nevirapine; severe or life-threatening rash has occurred in approximately 2% of patients receiving nevirapine[8].

Several early reports of death due to hepatic failure in HIV-infected pregnant women receiving nevirapine as part of a combination ARV regimen raised concerns that pregnant women might be at increased risk of hepatotoxicity from nevirapine compared with other ARV drugs[9-10]. Recent data challenge the notion that nevirapine is uniquely associated with increased hepatotoxicity during pregnancy[11]. In an analysis of two multicenter, prospective cohorts, pregnancy itself was a risk factor for liver enzyme elevations (relative risk [RR] 4.7; 5% confidence interval [CI], 3.4–6.5), but nevirapine use was not, regardless of pregnancy status[11]. Additional data from the same cohorts did not show any increased risk of hepatotoxicity in HIV-infected pregnant women receiving nevirapine-based combination ARV regimens versus non-nevirapine-based combination ARV regimens[12]. These data suggest that nevirapine is no more toxic in pregnant women than in nonpregnant women. Nevertheless, if nevirapine is used in pregnancy, health care providers should be aware of potential hepatotoxicity with or without rash and should conduct frequent and careful monitoring of clinical symptoms and hepatic transaminases (i.e., ALT and AST), particularly during the first 18 weeks of nevirapine use. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month, monthly through Month 4, and every 1–3 months thereafter (see the Hepatotoxicity section of the table on Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects in the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents). In patients with pre-existing liver disease, monitoring should be performed more frequently when initiating nevirapine and monthly thereafter[1]. Transaminase levels should be checked in all women who develop a

rash while receiving nevirapine. Patients who develop suggestive clinical symptoms accompanied by elevation in serum transaminase levels (ALT and/or AST) or who have asymptomatic but severe transaminase elevations (i.e., more than five times the upper limit of normal) should stop nevirapine and not receive nevirapine again in the future.

Hepatic toxicity has not been seen in women receiving single-dose nevirapine during labor for prevention of perinatal transmission of HIV[13]. Women who enter pregnancy on nevirapine-containing regimens and are tolerating them well may continue therapy, regardless of CD4 cell count.

References

1. Kontorinis N, Dieterich DT. Toxicity of non-nucleoside analogue reverse transcriptase inhibitors. *Semin Liver Dis.* 2003 May;23(2):173-182.
2. Bersoff-Matcha SJ, Miller WC, Aberg JA, et al. Sex differences in nevirapine rash. *Clin Infect Dis.* 2001 Jan;32(1):124-129.
3. Mazhude C, Jones S, Murad S, Taylor C, Easterbrook P. Female sex but not ethnicity is a strong predictor of non-nucleoside reverse transcriptase inhibitor-induced rash. *AIDS.* 2002 Jul 26;16(11):1566-1568.
4. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr.* 2004;35(5):538-539.
5. Stern JO, Robinson PA, Love J, Lanes S, Imperiale MS, Mayers DL. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. *J Acquir Immune Defic Syndr.* 2003 Sep;34 Suppl 1:S21-33.
6. Aaron E, Kempf MC, Criniti S, et al. Adverse events in a cohort of HIV infected pregnant and non-pregnant women treated with nevirapine versus non-nevirapine antiretroviral medication. *PLoS One.* 2010;5(9):e12617.
7. Peters PJ, Stringer J, McConnell MS, et al. Nevirapine-associated hepatotoxicity was not predicted by CD4 count ≥250 cells/muL among women in Zambia, Thailand and Kenya. *HIV Med.* 2010 Nov;11(10):650-660.
8. Boehringer-Ingelheim Pharmaceuticals Inc. Viramune drug label. March 25, 2011.
9. Lyons F, Hopkins S, Kelleher B, et al. Maternal hepatotoxicity with nevirapine as part of combination antiretroviral therapy in pregnancy. *HIV Med.* 2006 May;7(4):255-260.
10. Hitti J, Frenkel LM, Stek AM, et al. Maternal toxicity with continuous nevirapine in pregnancy: results from PACTG 1022. *J Acquir Immune Defic Syndr.* 2004 Jul 1;36(3):772-776.
11. Ouyang DW, Shapiro DE, Lu M, et al. Increased risk of hepatotoxicity in HIV-infected pregnant women receiving antiretroviral therapy independent of nevirapine exposure. *AIDS.* 2009 Nov 27;23(18):2425-2430.
12. Ouyang DW, Brogly SB, Lu M, et al. Lack of increased hepatotoxicity in HIV-infected pregnant women receiving nevirapine compared with other antiretrovirals. *AIDS.* 2010 Jan 2;24(1):109-114.
13. McKoy JM, Bennett CL, Scheetz MH, et al. Hepatotoxicity associated with long- versus short-course HIV-prophylactic nevirapine use: a systematic review and meta-analysis from the Research on Adverse Drug events And Reports (RADAR) project. *Drug Saf.* 2009;32(2):147-158.